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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Philip Buzby

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EXAMINER

BERTAGNA, ANGELA MARIE

ART UNIT

PAPER NUMBER

1637

MAIL DATE

DELIVERY MODE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/574,551	Applicant(s) BUZBY, PHILIP	
	Examiner ANGELA BERTAGNA	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 August 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7,9,10,13-16,18,21,23 and 26-30 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7,9,10,13-16,18,21,23 and 26-30 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>9/3/08</u> . | 6) <input checked="" type="checkbox"/> Other: <u>Notice to Comply</u> . |

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DETAILED ACTION

Status of the Application

1. Applicant's response filed on August 4, 2008 is acknowledged. Claims 1-7, 9, 10, 13-16, 18, 21, 23, and 26-30 are currently pending. In the response, Applicant amended claims 1, 4, 26, 29, and 30 and canceled claims 24 and 32.

The following objections and rejections have been withdrawn in view of the amendment: (1) the objection to the specification, (2) the objection to claim 24, (3) the rejection of claims 1-7, 9, 10, 13-16, 18, 21, 23, 24, 26-30, and 32 under 35 U.S.C. 112, second paragraph, and (4) the rejection of claims 24 and 32 under 35 U.S.C. 103(a).

Applicant's arguments regarding the remaining rejections made under 35 U.S.C. 103(a) have been fully considered, but they were not persuasive for the reasons set forth in the "Response to Arguments" section. Accordingly, this Office Action is made FINAL.

Information Disclosure Statement

2. Applicant's submission of an Information Disclosure Statement on September 3, 2008 is acknowledged. A signed copy is enclosed.

Sequence Rules

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent

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Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. The amendment to the specification filed on August 4, 2008 recites that the nucleic acid sequences appearing in Figure 1 are SEQ ID NO: 83-88. These sequences are not present in the Sequence Listing, which only has 64 sequences. Appropriate correction is required. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Specification

4. The disclosure is objected to because of the following informalities: Nucleic acid sequences greater than ten nucleotides in length are recited at pages 29-30 of the specification. These sequences must be identified by the appropriate SEQ ID NO: (see 37 CFR 1.821-1.825).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claims 1-7, 9, 10, 13-16, 21, and 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kwok et al. (US 6,180,408 B1; cited previously) in view of Tabor et al. (US 5,498,523; cited previously).

These claims are drawn to methods of inhibiting misincorporation of a terminator nucleotide in a single base extension reaction. The methods comprise treating a nucleic acid

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synthesis product with an inorganic pyrophosphatase to degrade inorganic pyrophosphate and thereby reduce the occurrence of pyrophosphorolysis.

Kwok teaches a homogenous genotyping method comprising PCR amplification, single base extension, and fluorescence polarization detection (see abstract, column 6, line 55 – column 7, line 10, and Figure 2 for a general description).

Regarding claims 1 and 26, the method of Kwok comprises:

(a) providing a product of a nucleic acid synthesis reaction comprising a nucleic acid template and a quantity of inorganic pyrophosphate (column 10, lines 29-47, where the PCR amplification step inherently generates inorganic pyrophosphate)

(b) purifying the nucleic acid synthesis product to obtain a purified reaction product (column 10, lines 48-58)

(c) combining the purified reaction product with a primer, a labeled terminator nucleoside, and a polymerase (column 10, line 60 - column 11, line 2)

(d) extending the primer by addition of the labeled terminator in a single base extension reaction (column 11, lines 2-5).

Regarding claims 2 and 27, the PCR amplification product obtained in the method of Kwok contains residual primers and nucleotides (see column 10, lines 48-58).

Regarding claims 3 and 28, Kwok teaches incubating the nucleic acid synthesis product with an exonuclease and an alkaline phosphatase to degrade the residual primers and nucleotides and then inactivating the enzymes (column 10, lines 48-58).

Regarding claims 5, 6, and 30, Kwok teaches enzyme inactivation (col. 10, lines 55-56).

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Regarding claim 7, Kwok teaches that the detectable label is a fluorescent label (see column 10, line 67 and column 11, lines 9-55).

Regarding claims 9 and 10, Kwok teaches detecting the label using fluorescence polarization (column 11, lines 9-55).

Regarding claim 13, Kwok teaches that the alkaline phosphatase is a bacterial alkaline phosphatase (column 6, lines 63-64, where HK thermolabile phosphatase is a bacterial alkaline phosphatase).

Regarding claim 14, Kwok teaches that the alkaline phosphatase is shrimp alkaline phosphatase (column 10, line 51).

Regarding claims 15 and 16, Kwok teaches that the exonuclease is exonuclease I or mung bean exonuclease (see column 6, lines 60-62 and column 10, line 52).

Regarding claim 21, Kwok teaches that the steps are performed in a single reaction container (column 3, line 65 - column 4, line 5).

Kwok does not teach incubating the nucleic acid synthesis product or the purified reaction product with an inorganic pyrophosphatase or a pyrophosphate removing enzyme to reduce the quantity of inorganic pyrophosphate present in the nucleic acid synthesis product or the purified reaction product.

Tabor teaches a method for conducting PCR in the presence of an inorganic pyrophosphatase (see column 3, lines 3-13 and column 4, lines 30-67). Regarding claims 1 and 26, Tabor teaches that the inclusion of an inorganic pyrophosphatase in the amplification reaction inhibits pyrophosphorolysis, which is detrimental to the primer extension step (column 3, lines 14-25). Tabor teaches that inhibiting pyrophosphorolysis improves the efficiency of the

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reaction (column 3, lines 24-27 and column 4, lines 63-67). Tabor teaches that these benefits are also applicable to primer extension reactions and sequencing reactions (column 3, lines 14-33 and lines 55-59).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Tabor to the method taught by Kwok. An ordinary artisan would have been motivated to include an inorganic pyrophosphatase in the PCR amplification and primer extension steps of the method taught by Kwok, since Tabor taught that inorganic pyrophosphatase degrades inorganic pyrophosphate produced by these reactions, thereby improving the efficiency of the reaction by inhibiting the detrimental pyrophosphorolysis reaction (column 3, lines 14-25). An ordinary artisan would have had a reasonable expectation of success in doing so, since Tabor taught that inorganic pyrophosphatase was commercially available (column 4, lines 51-56). Finally, regarding claims 4 and 29, it would have been *prima facie* obvious to add the exonuclease and alkaline phosphatase together with or after the addition of the inorganic pyrophosphatase, since section 2144.04 IV C of the MPEP states that any order of mixing ingredients is *prima facie* obvious. Thus, absent any secondary considerations, the methods of claims 1-7, 9, 10, 13-16, 21, and 26-30 are *prima facie* obvious over Kwok in view of Tabor.

7. Claims 18, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kwok et al. (US 6,180,408 B1; cited previously) in view of Tabor et al. (US 5,498,523; cited previously) and further in view of Jack et al. (WO 01/23411 A2; cited previously).

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These claims are drawn to the method of claim 1, wherein the terminator is an acyclo nucleoside terminator and the method is conducted using a polymerase that has a higher affinity for an acyclo nucleoside terminator than for a dideoxy terminator.

The combined teachings of Kwok and Tabor result in the method of claims 1-7, 9, 10, 13-16, 21, and 26-30, as discussed above.

These references do not teach that the terminator is an acyclo nucleoside terminator and the method is conducted using a polymerase that has a higher affinity for an acyclo nucleoside terminator than for a dideoxy terminator.

Jack teaches methods and compositions for improving the incorporation of chain terminating nucleotides by DNA polymerases (see abstract and page 9, line 30 - page 10, line 10). Regarding claims 18 and 23, Jack teaches that dye-labeled acyclo-NTPs are more readily incorporated by Family B archaeon DNA polymerases, such as Vent, Pfu, Deep Vent, and 9N, than dye-labeled ddNTPs (page 18, line 9 – page 19, line 14). Jack also teaches that increasing the efficiency of nucleotide terminator incorporation reduces costs, decreases background, and increases assay sensitivity (page 25, line 31 - page 26, line 2).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Jack to the method taught by Kwok. An ordinary artisan would have been motivated to substitute dye-labeled acyclo NTPs and a Family B archaeon DNA polymerase for the dye-labeled ddNTPs and AmpliTaq-FS taught by Kwok, since Jack taught that dye-labeled acyclo NTPs were more efficiently incorporated by a Family B archaeon DNA polymerase than ddNTPs (page 18, line 9 - page 19, line 14). Since Jack taught the more efficient terminator incorporation reduced costs, decreased background, and improved sensitivity

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(page 25, line 31 - page 26, line 2), an ordinary artisan would have been particularly motivated to substitute dye-labeled acyclo NTPs and a Family B archaeon DNA polymerase in the method of Kwok in order to obtain these advantages. An ordinary artisan would have had a reasonable expectation of success in using dye-labeled acyclo NTPs and a Family B DNA polymerase in the method of Kwok, since Jack taught that they were suitable for single base extension methods, such as the single base extension method taught by Kwok (page 26, line 25 – page 27, line 2). Thus, the methods of claims 18 and 23 are *prima facie* obvious over Kwok in view of Tabor and further in view of Jack.

Response to Arguments

8. Applicant's arguments filed on August 4, 2008 have been fully considered, but they were not persuasive.

Regarding the objection to the specification for reciting nucleic acid sequences unidentified by the appropriate SEQ ID NO, Applicant indicates that the correction to the table appearing pages 29-30 has been provided on a separate paper. This paper does not appear to be present in the Application file. Applicant is requested to resubmit the correction to pages 29-30.

Regarding the rejection of claims 1-7, 9, 10, 13-16, 21, and 26-30 under 35 U.S.C. 103(a) as being unpatentable over Kwok in view of Tabor, Applicant first argues that the combined teachings of Kwok and Tabor do not result in all of the claimed limitations. In particular, Applicant argues that Kwok does not teach the claimed step of producing a purified reaction product (see page 13 of the response). This argument was not persuasive, because the rejection is based on the combined teachings of the Kwok and Tabor. As discussed above, the teachings

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of Tabor would have suggested to an ordinary practitioner of the method taught by Kwok that inclusion of an inorganic pyrophosphatase in the nucleic acid synthesis reaction would provide the useful benefit of reducing the inhibition of primer extension due to pyrophosphorolysis. Inclusion of an inorganic pyrophosphatase in the nucleic acid synthesis reaction of Kwok, as suggested by Tabor, would result in the purified reaction product recited in claims 1 and 26. Furthermore, in response to applicant's arguments against the references individually (pages 13-14), it is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant also argues that there is no motivation to apply the teachings of Tabor regarding pyrophosphatase digestion to the method of Kwok, because Tabor teaches adding the pyrophosphatase enzyme to the amplification reaction rather than treating the resulting amplification product (pages 18-19). This argument was not persuasive, because the claims only require treating the product of a nucleic acid synthesis reaction with an inorganic pyrophosphatase to yield a purified reaction product. The claims do not exclude the method resulting from the combined teachings of Kwok and Tabor, wherein the nucleic acid synthesis reaction product is produced and treated with the pyrophosphatase enzyme present in the nucleic acid synthesis reaction mixture to produce the purified reaction product. Also, as discussed above, an ordinary artisan would have been particularly motivated to apply the teachings of Tabor to the method of Kwok, since Tabor expressly taught that pyrophosphatase enzymes could be included in sequencing or primer extension reactions to obtain the benefit of pyrophosphorolysis inhibition (column 3, lines 14-33).

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Applicant further argues that neither Kwok nor Tabor teaches inactivation of the pyrophosphatase or pyrophosphate removing enzyme as required by claims 6 and 30, respectively (see page 20). Applicant is correct that neither Kwok nor Tabor expressly teaches inactivation of the pyrophosphatase enzyme. However, since Kwok taught inactivation of the enzymes used to treat the nucleic acid synthesis product (*i.e.* exonuclease I and shrimp alkaline phosphatase) before conducting the single base primer extension reaction (column 10, lines 55-56), an ordinary artisan would have been motivated to inactivate the pyrophosphatase suggested by Tabor, recognizing that its activity, like the activities of exonuclease I and shrimp alkaline phosphatase, was no longer necessary. Attention is also directed to the recent Federal Circuit decision *Dystar v. Patrick Co.*, 80 USPQ 2d 1641, 1651 (Fed. Cir. 2006), which states:

Indeed we have repeatedly held that an implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the “improvement” is technology-independent and the combination of references results in a product or process that is more desirable, for example, because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient. Because the desire to enhance commercial opportunities by improving a product or process is universal - and even common-sensical - we have held that there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves. In such situations, the proper question is whether the ordinary artisan possesses knowledge and skills rendering him capable of combining the prior art references.

The *Dystar* court clarifies that motivation exists when the improvement made results in a more desirable product or process, and the issue devolves to whether the ordinary artisan possesses the knowledge rendering him capable of combining the references. Here, the ordinary practitioner holds a PhD and has years of experience in the art. As noted in *Dystar*, “If, however, as we have held as a matter of law, the level of skill is that of a dyeing process designer, then one can assume comfortably that such an artisan will draw ideas from chemistry and systems engineering – without being told to do so (*Dystar* at page 1653).” In this case, the ordinary

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artisan (*i.e.* a PhD scientist with years of experience), reading the Kwok and Tabor references would have recognized, without being explicitly told to do so, that any enzyme whose activity is no longer necessary following treatment of the nucleic acid synthesis product should be inactivated using standard methods prior to conducting the single base primer extension reaction taught by Kwok. Since Applicant's arguments were not persuasive, the rejection has been maintained.

Regarding the rejection of claims 18, 23, and 24 under 35 U.S.C. 103(a) as being unpatentable over Kwok in view of Tabor and further in view of Jack, Applicant argues that the teachings of Jack do not remedy the deficiencies in the primary combination of references - Kwok and Tabor (see pages 21-22). In view of the cancellation of claim 24, this rejection currently applies to claims 18 and 23. Applicant's argument was not persuasive, because as discussed above, the combined teachings of Kwok and Tabor result in all of the limitations of the instant claims 1-7, 9, 10, 13-16, 21, and 26-30. The teachings of Jack are only cited for those teachings relevant to dependent claims 18 and 23. Since Applicant's arguments were not persuasive, the rejection has been maintained.

Conclusion

9. No claims are currently allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ANGELA BERTAGNA/

Examiner, Art Unit 1637

/Kenneth R Horlick/

Primary Examiner, Art Unit 1637